A9

8. (amended) The drug release system for retinoic acid according to Claim 1, wherein the amphiphilic block copolymer comprises 1 ~ 20 wt% of poly-L-lactic acid-polyethyleneglycol di-block copolymer based on the total weight of the release system.

Kindly cancel claims 9 and 10 without prejudice or disclaimer.

Please add new claim 11, as follows:

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11. (new) A pharmaceutical composition for the prevention or treatment of diseases selected from the group consisting of head and neck cancer, skin cancer, lung cancer, breast cancer, cervical cancer, bladder cancer, and acute promyelocytic leukemia comprising an effective amount of the drug release system according to any one of Claim 1 through 8 as an active ingredient and a pharmaceutically acceptable carrier.

**REMARKS**

The claims were amended during the international phase of the application under Article 34. The amended claim set was filed as part of the response to the Written Opinion filed on February 26, 2001 with the IPEA (Australian Patent Office). A copy of the response to the Written Opinion including the claim amendments under Article 34 were filed with the instant §371 Patent Application filed on March 28, 2001. A copy of the Response to the Written Opinion and Article 34 claim amendment are enclosed for the Examiner's consideration.

The specification and claims have been amended to replace the word "amphoteric" with –amphiphilic--. As is well known in the art the word amphoteric refers to a material having both acid and base groups and the word amphiphilic refers to a material having both hydrophilic and hydrophobic groups. Applicants respectfully submit that the use of the word "amphoteric" in the

application as filed was a result of a mistranslation and that the substitution of amphiphilic for amphoteric in the specification and claims is fully supported by the application as filed. See particularly the Technical Field on page 1 and the working examples (which provide amphiphilic copolymeric materials not amphoteric materials).

Claim 8 has been amended to insert the full chemical name, as originally defined in the specification, for the abbreviation DiPLE. Claims 9 and 10 have been cancelled herein without prejudice to their subsequent presentation in this, or a related application. New claim 11 has been introduced and is supported by original claim 9. No new matter has been added by virtue of this amendment. Support for the amendment can be found throughout the specification.

The Examiner has objected to claim 5 because it depends from itself.

Claims 8-10 have been objected to under 37 CFR 1.75(c) as being in improper multiple dependant format.

Claims 5 and 8 as presented in the Article 34 amendment depend from claim 1. Claims 9 and 10 have been cancelled. New claim 11 depends from claim 1. Thus the objections to claims 5 and 8-10, regarding claim dependencies should be withdrawn.

The Examiner has objected to claim 8 because it includes abbreviations not defined in a parent claim.

Claim 8 has been amended to replace the abbreviation "DiPLE" which the full chemical name of the polymer, i.e., "poly-L-lactic acid-polyethylene glycol di-block copolymer," as defined in the specification at page 7, lines 14-15.

Claim 10 has been rejected under 35 U.S.C. §112, first paragraph, because the Examiner

asserts that the specification does not provide reasonable enablement for other conditions yet to be discovered to be treatable for retenoic acid.

Claims 9 and 10 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant believes to be the invention.

The Examiner asserts that claims 9 and 10 provide use of a drug release system but are indefinite for failing to recite a sue without an active positive step for the execution of the use.

Claims 9 and 10 were rejected under 35 U.S.C. §101 for the claimed recitation of a use without setting forth any steps involved in the process.

Applicants respectfully submit that the claims as amended are fully compliant with the requirements of 35 U.S.C. §101 and §112 including the requirements of 35 U.S.C. §112, first paragraph.

A brief discussion of the present invention may be beneficial before addressing the rejections presented by the Examiner in the outstanding Office Action.

The present invention provides drug delivery systems for the delivery of retinoic acid to patients in a controlled manner. The drug delivery systems of the invention comprises biodegradable microspheres comprising a biodegradable polymer such as PLLA, PDLA or PLGA, and an amphiphilic AB type di-block copolymer such as PLA-PEG or PLGA-PEG and at least one retinoic acid dispersed therein.

In contrast, none of the prior art references cited by the Examiner either alone or in combination teach or suggest combining the above two types polymers for the preparation of the microsphere. Further, the references do not specifically disclose the use of retinoic acid to the microsphere comprising the two types of polymers , particularly an AB type copolymer and a biodegradable polymer.

Further, the microspherecomprising a mixture of a block copolymer and a biodegradable polymer provided by the instant invention can control the release pattern of drug dispersed in the microsphere. The change of release pattern according to the function of the block copolymer is shown to be significant, particularly in the retinoic acid contained in the microsphere of the present invention. While not wishing to be bound by theory, Applicants believe that the acid-catalytic hydrolysis of the biodegradable polymer is accelerated when the microsphere is hydrated due to the hydrophilic PEG blocks of the block copolymer.

As shown in Fig. 2(a), the release pattern of all trans retinoic acid from the microsphere was dependent upon the contents of PLE and all trans retinoic acid. The cumulative release amount of all trans retinoic acid for 5 weeks was about 95%. As the contents of PLE and all trans retinoic acid were increased, the release pattern of all trans retinoic acid shifted from a first-order *to* a pseudo zero-order. The release pattern of such pseudo zero-order profile is necessary to provide a constant release rate of retinoic acid over an extended time periodwhile maintaining a substantially constant concentration of retinoic acid in the blood.

Claims 1-10 were rejected under 35 U.S.C. § 103(a) over Gref et al., (U.S. Patent 5,543,158) in view of Rodgers et al. (U.S. Patent 5,534,261).

The rejection is respectfully traversed.

As the reference is understood, Gref teaches a microsphere formed of a block copolymer which consists of poly(alkylene oxide) blocks and poly(lactic acid-co-glycolic acid) blocks. The Gref microspheres further comprise a series of polyalkylene glycol chains on the surface of the microsphere. However, Gref neither discloses nor suggests microspheres composed of a mixture of a biodegradable copolymer and an AB type di-block copolymer. Further, this reference does not explicitly disclose the application of retinoic acid to the microsphere.

In contrast, the present invention provides microsphere compositions in which the biodegradable polymer and the block copolymer are mixed together such that these microsphere compositions can be sterilized by ethylene oxide gas. The block copolymer component of the microsphere composition increases the crystallinity of the microsphere thereby preventing deformation of the microsphere during ethylene oxide sterilization procedures.

In contrast, conventional microspheres, such as those taught by Gref, which are prepared from a single biodegradable block copolymer, are stuck together after the sterilization by ethylene oxide gas, and so the conventional microspheres cannot be sterilized by ethylene oxide gas but can be by only γ-ray irradiation.

No C 13,158-64

Rodgers fails to overcome the limitations of the Gref disclosure. As the reference is understood, Rodgers discloses microspheres comprising all trans retinoic acid and a biodegradable polymer such as poly(dl-lactides), poly(dl-lactide-co-glycolides), or polycaprolactones. However, Rodgers never discloses or suggests combining an AB type di-block copolymer with the biodegradable polymer as claimed in the present invention.

Neither Gref, Rodgers or any combination thereof teach the microspheres of the present

invention. More particularly, the present invention would not have been obvious to one skilled in the art would not have been motivated by any combination of the cited references. Thus the drug delivery system for retinoic acid comprising a microsphere comprising a mixture of a block copolymer and a biodegradable polymer where the microsphere has a retinoic acid dispersed therein would not have been obvious to one skilled in the art based on Gref and Rodgers.

Thus claim 1 is patentable over the combined teachings of Gref and Rodgers. Claims 2-8 and 11 depend from claim 1 and are therefore also patentable over Gref in view of Rodgers.

Claims 1-10 were rejected under 35 U.S.C. § 103(a) over Cha et al. (U.S. Patent 5,665,428) in combination with Rodgers and further in combination with Lippman.

The rejection is traversed.

As the reference is understood, Cha ('428) teaches a microparticle comprising a polypeptide dispersed in a block copolymer capable of forming a hydrogel after injection into a patient or an aqueous media where a polypeptide is released from the hydrogel after injection. Cha ('428) neither discloses nor suggests any microparticle composition comprising a biodegradable polymer and an AB type block copolymer. Moreover Cha ('428) neither discloses nor suggests any microparticle compositions comprising a biodegradable polymer and an AB type block copolymer having at least one retinoic acid dispersed therein.

Rodgers fails to overcome the limitations of Cha ('428). Rodgers, as discussed *supra*, neither discloses nor suggests combining the AB type di-block copolymer with the biodegradable polymer as claimed in the present invention. Thus, no combination of Cha ('428) and Rodgers teach or suggest to one of ordinary skill in the art a drug delivery system comprising retinoic acid

dispersed in a mixture of an AB type di-block copolymer with the biodegradable polymer as provided by claim 1 of the present invention.

The disclosure of Lippman et al., fails to overcome the limitations of Cha ('428) in view of Rodgers. As the reference is understood, Lippman teaches the delivery of 13-cis-retinoic acid and interferon α-2a for the treatment of cervical cancer. Lippman neither discloses nor suggests drug delivery systems for the delivery of retinoic acid comprising microspheres composed of a mixture of AB type di-block copolymer and biodegradable polymer. Thus Lippman fails to overcome the limitations of the combined teachings of Cha ('428) and Rodgers.

Thus claim 1 is patentable over the combined teachings of Cha ('428) in view of Rodgers and Lippman. Claims 2-8 and 11 depend from claim 1 and are therefore also patentable over Cha ('428) in view of Rodgers and Lippman.

Claims 1-10 were rejected under 35 U.S.C. § 103(a) over Cha et al. (WO 97/15287) in combination with Rodgers and further in combination with Lippman (*J. National Cancer Institute*; 84(4):241-245; 1992).

The PCT publication of Cha et al. ('287) discloses an aqueous mixture of a biodegradable block polymer and a peptide/protein for delivery to a patient. The aqueous mixture is injected into a patient and the block polymer, which forms a hydrogel at body temperature, thereby trapping the peptide or protein in the gel matrix. The invention of Cha ('287) neither discloses nor suggests a microsphere in which the biodegradable copolymer is combined with AB type di-block copolymer, and further with retinoic acid as claimed in the present invention.

The disclosures of Rodgers and Lippman fail to overcome the limitations of Cha ('287).

Thus no combination of Cha ('287), Rodgers and Lippman teach or disclose the drug delivery systems of the invention comprising one or more retinoic acid dispersed in a microparticle composed of a biodegradable copolymer and an AB type di-block copolymer

Thus claim 1 is patentable over the combined teachings of Cha ('287) in view of Rodgers and Lippman. Claims 2-8 and 11 depend from claim 1 and are therefore also patentable over Cha ('287) in view of Rodgers and Lippman.

In view thereof, reconsideration and withdrawal of the rejections is requested.

It is believed the application is in a condition for immediate allowance.

Respectfully submitted,

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**VERSION MARKED TO SHOW CHANGES**

(Additions are underlined; deletions are bracketed.)

IN THE SPECIFICATION:

Kindly amend the paragraph starting at page 1, line 3, as follows:

The present invention relates to a controlled drug release system in which a certain ratio of retinoic acid (herein after referred to as "RA") is incorporated into a microsphere comprising biodegradable polymer and [amphoteric ]amphiphilic copolymer having both hydrophilic and hydrophobic groups.

Kindly amend the paragraph starting at page 2, line 9, as follows:

As another prior art reference for delayed retinoic acid release system, it has been reported that retinoic acid was released over 40 days by incorporating retinoic acid into a microsphere prepared from lactic acid and poly(lactic-co-glycolic acid), (hereinafter referred to as "PLGA") [see, investigative Ophthalmology & Visual Science 34, 2743-3751 (1993)]. The system was focused on the treatment of proliferative vitreoretinopathy. However, the microsphere prepared by this technique has a drawback that it is difficult to be dispersed into an aqueous phase. In addition, since ethylene oxide is impossible for applying gas sterilization, gamma-ray sterilization should be used. Even if, such gamma-ray sterilization is carried out on the microsphere, the molecular weight thereof is decreased. Further, this prior art system fails to teach the use of [amphoteric ]amphiphilic copolymer in controlling the dissolution rate of the microsphere and the release rate of retinoic acid.

Kindly amend the paragraph starting at page 3, line 1, as follows:

Another object of the present invention is to provide a controlled drug release system for retinoic acid which comprises microsphere in which the biodegradable polymer and [amphoteric ]amphiphilic block copolymer and retinoic acid incorportated into the microsphere.

Kindly amend the paragraph starting at page 5, line 15, as follows:

In one aspect, the present invention provides a controlled drug release system which comprises a microsphere in which biodegradable polymer and [amphoteric ]amphiphilic block copolymer are mixed together and retinoic acid incorporated into the microsphere.

Kindly amend the paragraph starting at page 7, line 6, as follows:

Any of polymeric surfactants may be preferably used without limitation provided that they are [amphoteric ]amphiphilic block copolymers having hydrophilic and hydrophobic groups, the example of which includes di-, tri- or multi-block copolymer or graft copolymer of the biodegradable polymer as mentioned in the above and polyethylene glycol. As such surfactant, polylactic acid-polyethylene glycol block copolymer is preferred, with poly-L-lactic acid-polyethyleneglycol di-block copolymer (PLLA-PEG, hereinafter, referred to as "DiPLE") or poly-L-lactic acid-polyethyleneglycol-poly-L-lactic acid tri-block copolymer (PLLA-PEG-PLLA, hereinafter, referred to as "TriPLE") being most preferred.

Kindly amend the paragraph starting at page 7, line 16, as follows:

It is obvious to those skilled in the relevant art that the mixing ratio of the above biodegradable polymer and the [amphoteric ]amphiphilic polymer within the microsphere can be suitable determined according to the desired effects such as for example release pattern of retinoic acid. However, it is desirable that the ratio be selected within the range of 1:0~100 part by weight based on the biodegradable polymer.

IN THE CLAIMS:

Kindly amend claims 1, 4, 5, and 8, as follows:

1. (amended) A controlled drug release system for retinoic acid characterized in that retinoic acid is incorporated into a microsphere prepared by mixing a biodegradable polymer and an [amphoteric ]amphiphilic AB type di-block copolymer together, wherein the retinoic acid is selected from the group consisting of all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, other retinoids and the mixture thereof.

4. (amended) The drug release system for retinoic acid according to Claim 1, wherein the [amphoteric ]amphiphilic block copolymer is poly-L-lactic acid-polyethyleneglycol or poly(lactic-co-glycolic acid)-polyethyleneglycol.

5. (amended) The drug release system for retinoic acid according to Claim 1, wherein the mixing ratio of the biodegradable polymer and the [amphoteric ]amphiphilic block copolymer is 1:0~100 part by weight.

8. (amended) The drug release system for retinoic acid according to Claim 1, wherein the [amphoteric ]amphiphilic block copolymer comprises 1 ~ 20 wt% of [DiPLE]poly-L-lactic acid-polyethyleneglycol di-block copolymer based on the total weight of the release system.

Kindly cancel claims 9 and 10 without prejudice or disclaimer.

Please add new claim 11, as follows:

11. (new) A pharmaceutical composition for the prevention or treatment of diseases selected from the group consisting of head and neck cancer, skin cancer, lung cancer, breast

cancer, cervical cancer, bladder cancer, and acute promyelocytic leukemia comprising an effective amount of the drug release system according to any one of Claim 1 through 8 as an active ingredient and a pharmaceutically acceptable carrier.